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| EXAMINER | |
|---|---|
| CLARK, D | |
| **ART UNIT** | **PAPER NUMBER** |
| 1633 | 12 |

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

**Commissioner of Patents and Trademarks**

# Office Action Summary

| Application No. | Applicant(s) |
|---|---|
| 08/993,564 | Newman, Stuart A. |
| **Examiner** | **Group Art Unit** |
| Deborah Clark | 1633 |

☒ Responsive to communication(s) filed on *Jun 16, 1999* .

☒ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *three* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

**Disposition of Claims**

☒ Claim(s) *1-55* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-55* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

**Application Papers**

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. § 119**

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

**Attachment(s)**

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

*--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---*

## DETAILED ACTION

1. The Examiner and Art Unit location of your application in the PTO have changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1633, examiner Deborah Clark.

### *Response to Amendment*

2. Applicant's amendment and response to the previous office action has been received and entered. Applicant's supplemental declarations have also been received and entered.

3. Claims 1-55 are now pending.

### *Claim Rejections - 35 USC § 101*

4. Claims 1-9 and 13-36 stand rejected, and newly submitted claims 37, 39-48, 52, and 54 are rejected, under 35 USC 101 as being directed to non-statutory subject matter for the reasons of record.

Applicants argue that the claimed embryos and animals are "made by man" and therefore within the scope of patentable subject matter under existing legal authority. Applicants argue that (1) subject matter "embracing a human being" is patentable under existing law and (2) the instant claims do not embrace human beings, but are limited to man-made chimeric embryos and the animals that develop from them. These arguments are not found to be persuasive.

Applicants first argue that the plain language of the statute, and controlling interpretations of that statute such as Diamond v. Chakrabarty, 447 U.S. 303 (1980), and State Street Bank & Trust Co. v. Signature Financial Group, 149 F.3d 1368 (Fed. Cir. 1998), support the patentability of subject matter embracing a human being. From their review of the law, Applicants conclude that

> [i]t is for Congress--not the courts or the PTO--to set forth any limitations on patentable subject matter. Congress has not established any limitation based on subject matter that 'embraces a human being.' The Commissioner lacks the authority to impose one under Section 101. Whether or not the PTO believes Congress intended to bar patentability of inventions that embrace a human being is not the issue. Congress has not done so expressly and the PTO has no authority to fill the gap.

The examiner does not agree with either Applicants' reading of the relevant law or their view of the PTO's authority to interpret the law. The PTO is obliged to follow the intent of Congress when administering the patent laws. Neither the statute itself nor its legislative history contain an explicit statement of whether § 101 was intended to encompass human beings. However, the intent of Congress can be inferred by considering § 101 in the context of the larger legal framework of which it is part. At a minimum, grant of patent rights in human beings would be inconsistent with the constitutional right to privacy and with other provisions of Title 35 of the U.S. Code. Thus, when the terms of § 101 are construed in the context of an integral system of legal rights, it can be inferred that Congress did not intend that patent protection be extended to subject matter that embraces a human being.

A patent issued by the PTO confers on the patentee the right to exclude others from, inter alia, making the claimed invention. If the "claimed invention" were permitted to encompass a human being or a viable human embryo, this right to exclude others from making the invention would conflict with the constitutional right to privacy enunciated by the Supreme Court. That is, the reproductive choices of a human being who was encompassed by the patent claims, or a human being who arose from a patented embryo, would be subject to the patentee's legal right to exclude others from "making" further patented human beings or embryos. However, reproductive decisions are at the heart of the constitutional right to privacy. See, e.g., Griswold v. Connecticut, 381 U.S. 479 (1965) (state law banning use of contraceptives infringes constitutional right to privacy); Eisenstadt v. Bard, 405 U.S. 438, 453 (1971) ("If the right to privacy means anything, it is the right of the individual, married or single, to be free from unwarranted governmental intrusion into matters so fundamentally affecting a person as the decision whether to bear or beget a child."); Roe v. Wade, 410 U.S. 113 (1973) (state law allowing abortion only to save the life of the mother violates the Due Process Clause of the Fourteenth Amendment). If the government were to grant a patentee the legal right to control the reproductive choices of another human being, that grant would violate the constitutional right to privacy enunciated by the Supreme Court. Since grant of patent rights in a human being would

violate the constitutional right to privacy, it may be inferred that Congress did not intend to include human beings within the scope of § 101[1].

In addition, to construe § 101 to allow patentability of human beings would conflict with the other provisions within Title 35 of the United States Code. For example, 35 U.S.C. § 271(g) provides that it is an act of infringement to import products made abroad using a process patented in the United States. Patentable processes include methods of performing surgery. If a human being were regarded as a "product," under the patent laws, the product of a patented surgical process would be a surgically altered human being. Thus, a U.S. resident who went abroad, had surgery (where the surgical procedure was patented in the U.S.) and then imported himself (i.e., returned) to the U.S. would be liable under 35 U.S.C. § 271(g) for patent infringement based on his importation of a product made by an infringing process. However, a patient undergoing the same surgery within the U.S. would not be liable for infringement (although the doctor performing the surgery might be). Thus, treatment of human beings as "products" under the

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[1]In addition, the right to exclude others from "using" the claimed invention may conflict with the prohibition of Amendment XIII on involuntary servitude. A patent that included a human being within the scope of the claims would permit the patentee to exclude all others from "using" that human being. To "use" means to "put into action or service : avail oneself of : EMPLOY." Meriam Webster's Collegiate Dictionary, 10th Edition (1997). Thus, a patent could give the patentee a legal right to exclude all others from employing the patented human being. Such a situation would be tantamount to involuntary servitude and therefore prohibited by Amendment XIII. See Clyatt v. United States, 197 U.S. 207, 218 (1905) ("[I]nvoluntary servitude [is] a state of bondage; the ownership of mankind as a chattel, or at least the control of the labor and services of one man for the benefit of another, and the absence of a legal right to the disposal of his own person, property and services."). In fact, the patented human being could conceivably be excluded by the patentee from "using" himself, i.e., self-employment, an absurdity that reinforces the conclusion that Congress did not intend to allow patenting of human beings.

patent laws creates anomalies that demonstrate that Congress did not intend human beings to be treated as mere products under the patent laws.

The contradictions that would arise from extending patent protection to subject matter embracing a human being indicate that Congress could not have intended to include human beings within the scope of patentable subject matter. The PTO has long recognized this intent by rejecting claims that encompass a human being under 35 USC § 101, and by requiring that claims drawn to animals be expressly limited to "non-human" animals . Despite the lack of an express exception for human beings in § 101, a claim that encompasses a human being is drawn to non-statutory subject matter.

Applicants' position that the PTO lacks the authority to interpret the patent laws beyond their express statutory terms is untenable. The PTO performs a quasi-judicial function in determining patentability, and is regularly called upon to interpret the law in its case-by-case review of patent applications. See, e.g., Western Elec. Co. v. Piezo Tech., 860 F.2d 428, 431, 8 USPQ2d 1853, 1856 (Fed. Cir. 1988) (citing Butterworth v. United States ex rel. Hoe, 112 U.S. 50, 67 (1884) ("That it was intended that the Commissioner of Patents, in issuing or withholding patents ... should exercise quasi-judicial functions, is apparent from the nature of the examinations and decisions he is required to make.")). The PTO is well within its authority to interpret the scope of § 101 in light of established principles of statutory construction.

Applicants also argue that, even if human beings were properly excluded from patentable subject matter under § 101, "[a]ll of the subject matter of the present claims is drawn to chimeras

and, therefore, by definition to subject matter that is not human." However, claims 37 and 52 explicitly recite that the chimeras are human. Applicants argue that "a proportion of human cells in an organism does not make that organism a human being." This argument is not persuasive with respect to the instant claims, for several reasons. First, the specification sets forth no minimum or maximum quantities (percentages) of human cells that are possessed by the claimed chimeras. When given their broadest reasonable interpretation, therefore, the claims embrace chimeric embryos and animals that are fully human but for 1% or less of their cells being derived from another species. Although a chimeric organism may be obviously non-human in an extreme case (e.g., 99% non-human cells, 1% human cells) and of ambiguous humanity in other cases (50% human cells, 50% non-human cells), the claims contain no limitations excluding a chimera having, e.g., 99% human cells. Such a chimera would be considered a human being since even human beings whose bodies contain cells from different species are not considered non-human. See, e.g., Groth et al., Journal of Molecular Medicine, Vol. 77, pages 153-154, January 1999 (Xenoislet Transplantion: Experimental and Clinical Aspects [pig-to-human]); Los Angeles Times, Jan. 12, 1993 at A15 (baboon liver transplanted into human). Despite the controversial nature of xenograft and xenotransplant therapy, no one has suggested that such patients are non-human.

Finally, Applicants argue that the PTO routinely grants patents on subject matter which Applicants believe to "embrace a human being" to the same or greater extent as the instantly claimed invention. Applicants argue that the "present rejection is novel and unprecedented and this is the teeth [sic] of the Commissioner's established practice and procedure." Applicants cite

two research papers describing engraftment of human hematopoietic cells in mice and sheep. Applicants conclude that these mice and sheep, although containing human cells, are not considered to be human beings and that "[t]he Office ... has regularly granted patents on such inventions," although no such patents are cited. Applicants argue that the instantly claimed chimeras, although containing human cells, should likewise not be considered to be human beings.

This argument is also not persuasive. Each application is evaluated on its own set of facts. Every application presents its own unique set of facts that raise a unique set of questions relating to patentability. This case presents a set of facts that raise questions regarding the patentability of the claimed subject matter under § 101 and the instant rejection is therefore justified, regardless of what rejections may or may not have been made in other cases. See In re Wertheim, 541 F.2d 257, 264, 191 USPQ 90, 97 (CCPA 1976) ("[I]t is immaterial in ex parte prosecution whether the same or similar claims have been allowed to others."). Moreover, Applicants have cited no issued patent to support their contention that "[t]he Office ... has regularly granted patents on such inventions" and the examiner is not aware of any issued patents claiming chimeric animals that embraces human beings. Thus, there is no evidence of an established PTO policy that is contradicted by the present rejection.

The limitations of newly introduced claims 39-48, limiting the claimed embryos to those that are viable for only a limited period of time or that are terminated after a limited period of time, do not overcome the rejection. Although the exclusive rights granted by a patent on the inventions of these claims would lapse after the recited periods of time, the instant claims would

still provide the patentee with a legal right to interfere with the reproductive choices of a human being that carried such an embryo. For the government to grant such a right to the patentee would violate the constitutional right to privacy. See the discussion of Griswold, Roe, and Eisenstadt, supra.

In conclusion, the above recited claims stand or are rejected under 35 USC 101 as being directed to non-statutory subject matter for reasons of record.

***Claim Rejections - 35 USC § 102***

5. Claims 1, 2, 5-7, 13, and 16 stand, and newly presented claims 38-48, 53, and 54 are, rejected under 35 USC 102(b) as being anticipated by Zanjani et al. or Almeida-Porada et al. for reasons of record.

Applicants argue that the organism of Zanjani et al. is unambiguously of one species. The examiner does not understand this statement. The organism of Zanjani et al. is a chimera. A chimera is an organism made up of two or more tissues of different genetic composition. Applicants argue that the present invention claims a true chimera. Again this is not understood. Applicants argue that the organisms disclosed by Zanjani et al. or Almeida-Porada et al. do not have composite morphology and multi-tissue chimerism of the early embryo chimeras and represent xenograft models. However, applicant's claims do not recite that the chimera would have multi-tissue chimerism or composite morphology. Further, the organisms of Zanjani et al.

and Almeida-Porada et al. have composite morphology because their structure is clearly from two distinct sources.

Applicants argue that the present invention describes chimeric embryos containing human cells, where aggregation of totipotent cells of two or more species is performed. However, none of the rejected claims have these limitations. All the limitations of the claims are taught by Zanjani et al. and Almeida-Porada et al.

Therefore, the above recited claims stand or are rejected under 35 USC 102(b) as being anticipated by Zanjani et al. or Almeida-Porada et al. for reasons of record.

6. Claims 1, 2, 5-7, 13, 16, 28, 29, and 32-34 stand, and newly presented claims 38-48, 53, and 54 are, rejected under 35 USC 102(b) as being anticipated by Pixley et al. for reasons of record.

In response to this rejection applicants argued this rejection together with the above discussed rejection. No statements were made regarding Pixley et al. specifically other than those addressed above. Therefore, the rejection is maintained for reasons of record as addressed above.

7. Claims 10-12 stand, and newly presented claims 50-51 are, rejected under 35 USC 102(b) as being anticipated by Cheng et al. for reasons of record.

Applicants argue that cells derived from chimeras are known to differ in immunological properties from equivalent cells in non-chimeric animals. However, this depends upon the type of cell. Certainly immunologically, the cells contributing to the chimerism of the animal would be recognized as self. However, this is in terms of the chimera as a whole or cells of the immune

system. Cells not involved in immune responses, such as hepatocytes or epithelial cells, would have the characteristics of the species of cell from which that particular cell was derived.

Applicants argue that the statement "the animals that are prepared from the chimeras may not harbor any transgenes if the germ cell from which the animals are derived did not harbor a transgene" is not correct because the claims do not rely on breeding techniques but rather specify that the animals are developed from chimeric embryos. It is noted that claim 10 has been amended to recite that the cell line is *generated* from a chimeric embryo (see below). However, the point is that each cell of the embryo may not have the transgene. Unless all the cells that were "aggregated" when making the chimeric embryos had the transgene then the chimeric embryo would be mosaic. Therefore, one could easily envision a cell-line that would not have the transgene.

In conclusion the above recited claims stand or are rejected under 35 USC 102(b) as being anticipated by Cheng et al.

8. Claims 10-12 stand, and newly presented claims 49 and 51 are, rejected under 35 USC 102(b) as being anticipated by American Type Culture Collection Catalog of Cell Lines for reasons of record.

In response to this rejection applicants present the argument addressed above. Therefore, the claims stand or are rejected for reasons of record as addressed above.

9. Claims 13-18 stand, and newly presented claims 53 and 54 are rejected under 35 USC 102(b) as anticipated by Bradley et al. for reasons of record.

Applicants argue that because the claimed animals are derived from chimeric embryos they differ in form, appearance, and biology from a non-chimeric transgenic animal. However, as stated previously the claims are not clearly directed to a chimeric animal, but merely an animal derived from a chimeric embryo. The animal derived therefrom is not necessarily chimeric. If the claim is read to encompass the descendant of the embryo then the animal is not chimeric, but is of the species that contributed to the germ cell. The chimeric embryos encompassed by the claims may also be indistinguishable from an animal of the prior art because the recited human cells are not required to contribute to any particular tissue or tissues and may actually contribute very little to the animal as a whole such that the animal would be indistinguishable from an animal of the second species. Therefore, the claims stand rejected for reasons of record.

***Claim Rejections - 35 USC § 103***

10. Claims 1, 2, 5-7, 19, 20, 23-25, 28, 29, and 32-34 stand, and newly presented claims 37-48 are rejected under 35 USC 103 as being unpatentable over Gustafson et al. for reasons of record.

Applicants argue that Gustafson et al. does not teach or suggest chimeric embryos containing human cells. However, as stated in the previous office action Gustafson et al. provided the motivation to make chimeric embryos with human cells.

Applicants argue that the invention cannot be unpredictable and obvious. However, this is not the case. As set forth in the previous office action the unpredictability is based upon

formation of an independent animal as taught in the specification, herein (see below) this rejection is maintain based upon the ability of the embryo to form a cooperative entity. However, each of the rejected claims is directed to chimeric embryos and would encompass the cell aggregates from the time of aggregation. Therefore, given the teaching of Gustafson et al. It would have been obvious to one of ordinary skill in the art at the time the invention was made to make a cell aggregate comprising human cells, though it's viability would likely be limited.

11. Claims 1, 8, 9, 19, 26-28, and 35-36 stand, and newly presented claims 37-48 are rejected under 35 USC 103 as being unpatentable over Watanabe et al. in view of Robertson et al.

Applicants argue that neither Watanabe et al. or Robertson et al. disclose the present invention because neither discloses chimeric embryos containing human cells. This is true, however, as stated in the previous office action the prior art provides motivation and a reasonable expectation of success in making chimeric embryos. Applicants argue further that the art does not disclose the specific uses in directly studying human development as described in the specification. However, the claims are directed to products not methods of using the products. Whether the art discloses uses as implied by the specification is irrelevant to the novelty or obviousness of the product claims.

Applicants argue that the examiner relies on hindsight afforded only by the present application. It must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was

made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

Applicants argue that the ability to make the claimed chimeras has only recently become possible due to advances in technology. In support thereof applicants cite statements made by the examiner in regard to enablement of the invention. However, the claims are not interpreted under the same standards in regards to 35 USC 112, 1st paragraph which requires enablement of both how to make and how to use, as under 35 USC 103. Under 35 USC 103, the claims are interpreted to their broadest reasonable scope which includes the making of embryos which may be viable for very short periods of time not even one cell cycle.

### *Claim Rejections - 35 USC § 112*

12. Claims 39-48 and 55 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The instant specification does not provide support for the newly advanced claims 39-48 which require that an embryo be viable no longer than a specific amount of time or be terminated on or before a specific day of age. The specification describes human/non-human animal chimeric animals or embryos which will develop into animals (see, e.g. pages 7-9 of the specification). The specification does not recite any limitation upon the length of time that an embryo would be

viable. There is no explicit or implied support for embryos which are viable no longer than 10 days, 12 days, 14 days, 21 days, or 180 days. "Viability" as interpreted in the art implies that the embryo lives on its own without human intervention. Thus, the embryo of claims 39-43 would die on its own at the specified time. "Termination" could mean either the embryo dies on its own (for example due to genetic programming), or dies as a result of human intervention. Thus, the embryo of claims 44-48 would also die on its own. Because nothing in the specification implies that the embryo could not develop into a chimeric embryo, there is no explicit or implied support for the claimed embryos which are viable for no longer than a specific time or which are terminated at a specific time.

The specification does not provide support for newly advanced claim 55 which requires that a resultant animal display a specific phenotype. The specification does not set forth any phenotypic characteristics that a resultant animal would have. The specification merely describes a chimeric animal in general terms and does not describe any phenotypic characterization of the claimed chimeric animal. Specifically there is no recitation that the chimeric animal would be bipedal, have opposable thumbs, have the ability to reason, be able to communicate using sign language, or have the ability to communicate using speech. Therefore, the instant specification does not provide written description of the claimed invention.

13. Claims 1-36 stand, and newly presented claims 37-55 are, rejected under 35 USC 112, 1st paragraph for reasons of record.

Applicants argue that the prior art provides an enabling disclosure of the claimed invention. Applicants cite Fehilly et al. and Meinecke-Tillman and Meinecke as enabling. Both Fehilly et al. and Meinecke et al. disclose "geeps". First, it is noted that the "geeps" were made from two closely related species, sheep and goats. Sheep and goats have similar development pathways and gestational timing. Further, it is not clear as to how applicants can state *a priori* that the technology was available only recently and then refer to art of 15 years prior as enabling. Finally, as stated in the prior office action, in the "geeps" it was completely unpredictable as to how the cells taken from the two species would contribute to the resultant chimera. Furthermore, the showing of viable "geeps" does not enable any other interspecies chimera because each species has divergent developmental aspects that would make its use in chimeras unpredictable. For instance, human embryos must secrete chorionic gonadotropin in order to maintain the pregnancy. How would one of skill in the art ensure that the appropriate cells contributed to the chimera such that this hormone was secreted? How would one of skill in the art know whether this hormone would be needed if the surrogate mother was non-human? These questions, and others, are of paramount importance in determining whether interspecies chimeras could be made with human cells and have yet to be answered.

Another method of making the claimed chimeras requires the use of ES cells. Applicants cite to Martin for establishment of mouse ES cells and Thomson et al. for disclosure of rhesus monkey ES cells. However, certain claims require use of human ES cells which were not known at the time of filing. At the time of filing only mouse and rat ES cells had been disclosed which

had been demonstrated as useful for making a chimeric animal. Further, the rhesus monkey ES cells had not, and have not, been demonstrated as being true ES cells, i.e. contributing to the germ cells. Therefore, in addition to the interspecies conflicts, the starting materials are only known to be available for the mouse and rat. This means that if the first cells were human, and not required to be ES cells, then the second species would need to be mouse or rat if this method were used. Humans are not closely, but rather are very distantly, related to mouse and rats. Specifically the species split at the order level: meaning they share the kingdom, phylum, and class, but not the order, family, genus, or species.

The third technique as cited by applicants also requires ES cells and would be subject to the same aspects as described above.

Applicants recite aspects of development that all early mammalian embryos undergo. However, there are many more differences that would need to be overcome. For instance, a mouse makes use of an embryonic disc whereas a primate forms an egg cylinder. Primate species must secrete chorionic gonadotropin, other species do not. The later in development the more pronounced the differences. For instance, a mouse is born after only 21 days of gestation whereas humans are gestated 9 months. Therefore, the timing of maturity of each system would be in chaos.

Art which discloses intraspecific mice are not persuasive to show that the claimed invention is enabled because the chimeras are made of mouse-mouse. One could not extrapolate

this procedure to include chimeras made with animals of two different species, or chimeras made with animals other than mice.

Applicants cite Stern and Rossant et al. for disclosure of mouse-rat and mouse-mouse chimeras. However, as stated above, such chimeras cannot be extrapolated to other species, especially where the two species used to make the chimera are distant.

Applicants argue that the results of the art as recited demonstrate that the technology is "robust". The examiner does not agree. Very few species have been demonstrated as useful in making interspecies chimeras, mouse, rat, sheep, and goat. One of skill in the art would not readily assume this to mean that any species of animal could likewise be successful when given the differences found between the species, especially where the two species are distant.

Applicants argue that the literature does not indicate that mixture of embryo cells from three species would immediately die. However, a chimera made using cells of three subjects would face all the issues discussed previously, but compounded to extend beyond just two species. Applicants state that the existing knowledge is that three cell types would cooperate with one another in building embryonic tissues and organs. However, this opinion is merely speculative. The examiner is aware of no knowledge in the art regarding a three species chimera. Applicants provide no data that such a chimera has even been made.

Applicants state that the three species interactions would provide a valuable tool, however, before such can become a valuable tool it must be able to be produced. As stated

above, and in the previous office action, the specification does not enable the making of such a chimera.

Applicants argue that predictability should not be a condition of patentability. Predictability is determined with regard to the specific invention and it's implied use. In the instant case the unpredictable outcome would preclude one of skill in the art from using the claimed invention (see the previous office action). One of skill in the art must be enabled to make and use the claimed invention.

Applicants cite US Patent No. 4,736,866 and argue that the granted claims have numerous unpredictable outcomes. However, as stated above, each invention is considered on it's own merits.

Applicants argue that the predictability, reproducibility, or "quality control" requested is not appropriate and is not required for similar invention. However, predictability and reproducibility are factors to considered in a determination of enablement. As to whether they are required in similar inventions is not clear because the examiner is not at liberty to discuss other applications with applicants.

Applicants argue that variations in the degree of chimerism, the similarity of the genotype to the gestational environment, and other uncontrolled factors would be a basis for using the claimed invention as a model for developmental biological and immunological research. However, in order to use the chimera for these purposes they must be viable for at a period of time sufficient for such research. As was set forth in the previous office action, it is not

predictable or expected that the chimeras would develop into an independent animal. Further, the embryo must be viable for a period sufficient to establish chimerism in order to perform said research. Therefore, in order to be enabled to use the embryo one would have to be enabled to make an embryo which has progressed to a stage such that the cells of both species were recognized as self and were functioning in a cooperative manner as one entity. As set forth in the previous office action such is not the case.

Applicants argue that useful information may be obtained without a requirement for implantation of a chimeric embryo and that much work is done *in vitro*. Applicants further argue that the survival rate is irrelevant for certain embodiments. However, as stated above, in order to obtain useful information the embryo must survive long enough to ensure that the cells are cooperating, i.e. no longer functioning separately, but together in the formation of one entity. It is not clear that distant species would pass this level of viability and even with closer related species it is unpredictable that primate cells would be viable to that point because no chimeras have been made using primate cells and only a limited number of species has ever been used.

Applicants argue that some degree of unpredictability is desirable and that some experimentation is allowed as long as it is not undue. However, in the instant case the amount of experimentation needed to practice the claimed invention is considered undue for reasons of record and above.

Applicants argue that the examiner is misinterpreting the term "viable" and state evidence that the term simply means "not dead". However, the claims are interpreted based upon the

disclosure of the specification. Such point is well taken. However, as addressed above, in order to use the claimed embryos the embryos must survive long enough that the cells cooperatively function as one entity. The specification does not enable one of skill in the art to make or use such an embryo for reasons of record and above.

Applicants argue that fecundity is not a basis for rejecting the claims and is not a requirement for patentability under 35 USC 101. However, this rejection is made under 35 USC 112, 1st paragraph, not 101. Certain of the claims are directed to or encompass descendants of the chimeric embryos (claims 13-18 and 52-55). Therefore, fecundity is a proper consideration.

Applicants argue that the descendants of chimeric animals are claimed not because they themselves would be chimeric, but because the germ cells would be altered because of their origin within a chimeric organism. In support applicants cite Sumantri et al., however, this reference is not of record and has not been considered. Nevertheless, the specification does not teach how one would use a non-chimeric animal with an altered germ cell. In addition, the specification does not enable one of skill in the art to make such an animal, for reasons above and in the prior office action and because there is no way to predict what alteration, if any, would be present in the germ cell.

Applicant's amendment to limit the second animal species to a mammal in certain of the claims is noted. However, the claims continue to encompass a wide diversity and claims 10-18 were not so limited, or the claims that depend therefrom. For instance, as addressed above, a human-mouse chimera represents a wide diversity which would likely not be viable long enough

to become a cooperative entity. Other mammalian species are just as diverse to humans, for instance, a duckbill platypus, which doesn't even give birth viviparously, sea mammals, which have distinctive organs that humans do not have, etc.

Applicants argue that germline chimerism is not the defining feature of ES cells. However, true ES cells must be able to contribute to the germ cells (see Nichols et al. at page 1341, Clark et al. at page 250, and Kollias et al. at page 92, each attached hereto).

Applicants argue that ES cells are enabled for use in the claimed invention because several species of ES cells have been documented. However, to date, only the mouse and rat ES cells have been shown as contributing to a chimeric animal. Wheeler et al. (as cited by applicants) demonstrated that porcine ES cells contributed to germ cells, but to date has been unsuccessful in making a chimeric animal. Thomson et al. has not made chimeric monkeys, nor have the rabbit ES cells been used to make chimeric rabbits. Therefore, the only ES cells that are known to date which could be possibly used in the claimed invention are mouse or rat.

Applicants argue that even human ES cells are now known. First, it is pointed out that the reportedly derived human ES cells have not been proven as true ES cells and have not been demonstrated as contributing to germ cells. Further, as noted by applicants, these data were published after the filing date of the instant application. The invention must be enabled at the time of filing.

In conclusion, the claims stand or are rejected under 35 USC 112, 1st paragraph for reasons of record.

14. Claims 1-36 stand, and newly presented claims 37-55 are rejected under 35 USC 112, 2nd paragraph for reasons of record.

Claims 1-36 and 37-55 remain indefinite due to their recitation of the phrase "chimeric embryos". Applicants write that they consider the term to mean a viable embryo, not necessarily able to become an independent animal. However, it is not clear how one is to determine when the aggregated cells actually become a viable embryo, i.e. functioning cooperatively as one entity. Therefore, the recitation remains indefinite.

Claim 13, and the claims which depend therefrom, remain indefinite due to the recitation of the phrase "developed from". Applicant's argument is not persuasive because in this instance as used it is not clear whether the claim refers to development in an embryonic sense or reproduction.

Claim 10 has been amended to recite "a cell line generated from a chimeric embryo". This phraseology remains indefinite because it is not clear as to what was done in this "generation". Generate means to bring into being, however, if the cells come from a particular source they are not actually brought into being. It is recommended that applicants replace this term with the word "isolated". Applicants argue that the cells would be distinguishable from cells from non-chimeric animals because of their immunology. However, this argument is addressed under the section entitled 35 USC 102, briefly it would depend upon the type of cell and it's location with regard to cells of the other species and the degree to which each species contributes to the chimera.

Further, the claims have no limitation regarding such characteristics. For these reasons the claims which depend from claim 10 are also indefinite.

Claims 44-48 recite that the chimeric embryo is "terminated" on or before a specific day. This recitation is vague because the specification provides no definition for the term. The term can be defined in at least two ways. Either the embryo spontaneously terminates on its own (for example due to genetic programming), or the embryo is terminated by human intervention. One of skill in the art would not be reasonably apprised as to the meets and bounds of the claim because it is not clear as to which definition of the term applicants rely upon.

***Conclusion***

15. No claim is allowed.

16. Claims 3, 4, 21, 22, 30, 31, 52, and 55 are free of the prior art of record. Claims 3, 4, 21, 22, 30, and 31 require the use of human ES cells. At the time of filing human ES cells were not known and to date reports of human ES cells have not been validated. Claim 52 is free of the prior art of record because the claim requires that the animal be a human and the prior art does not disclose a human which is chimeric with another non-human species. Claim 55 is free of the prior art of record because the claim requires that the chimera have certain phenotypic characteristics which would not have been predictable based upon the prior art.

17. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Deborah Clark whose telephone number is (703) 305-4051. The examiner can normally be reached on Mondays-Fridays from 7:10 a.m. EST to 3:40 p.m. EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jasemine Chambers, can be reached on (703) 308-2035. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Deborah Clark

DEBORAH J. CLARK
PATENT EXAMINER

Jasemine C. Chambers

Jasemine C. Chambers
SPE
TC 1600